Remarks

Claims 1-25 are pending. Claims 1, 7, 12, 13, 14 and 19 have been amended to clarify the claimed subject matter. No new matter or limitations have been added.

The claimed methods and compositions are directed to selectively delivering molecules to the nucleus of endothelial cells of the large vessels, by administering a conjugate of (1) an agent binding selectively to endothelial protein C receptor (EPCR) which promotes uptake by the cell and transfer into the nucleus and (2) the molecule to be delivered to large vessel endothelial cells. The conjugate binds to the EPCR, the conjugate is endocytosed, and the molecule is thereby delivered to the cytoplasm or to the nucleus of the large vessel endothelial cells (see claim 1 as originally filed and the Examples in the specification). The conjugate may be delivered by directly contacting the endothelial cells of large vessels with the conjugate or by catherization within blood vessels formed by the endothelial cells (page 10, lines 15-18).

Telephonic Interview of May 7, 2003

The Applicant's thank the Examiner for granting the telephonic interview of May 7, 2003. Claims 1-25 were discussed with regard to lack of enablement. The applicant's representative, Patrea Pabst, requested that the references submitted with the response mailed on February 4, 2002, be reviewed with regard to enablement issues raised by the Examiners handling the case (Neither the previous examiner, William Sandals, nor the present examiner has provided any substantive comments related to all of the previously submitted references). In response, Examiner Kaushal issued an interview summary explaining why one reference

(Baumgartner *et al.*) does not provide support for enabling the presently claimed invention. While the Applicants respectfully disagree with the Examiner's assertion (please see below), the Examiner again failed to provide any substantive comments with regard to the *other four references and abstracts* submitted on February 4, 2002 (an article by Lode *et al.* (*Proc. Natl. Acad. Sci.*, Vol. 95, pp. 2475-2480, March 1998); an abstract by Nguyen *et al.*,(*Cancer Gene Ther.*, 1997, May-June); an abstract by Watanabe *et al.* (*Nippon Rinsho*, March 1998, 56(3):724-730); and an abstract by Feero *et al.*, (*Gene Ther.*, 1997, 4(7)664-674).

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-25 were again rejected under 35 U.S.C. § 112, first paragraph, as not enabled for all agents which selectively bind to EPCR. Applicants respectfully traverse this rejection if applied to the amended claims.

The invention is the discovery that molecules which are bound by the EPCR on cells are taken up by the cell and can thereby be transported into the nucleus. This is demonstrated in the application with respect to one molecule, an antibody to the receptor. The examiner seems to accept that an antibody conjugate is enabled. The issue is with respect to other molecules which bind to the EPCR. However, there is no evidence that such data is not predictive of efficacy for other molecules which bind to this receptor. It is well established there it is not enough for the examiner just to assert that the claims are not enabled. He must provide some evidence for why *one skilled in the art would not think it was not enabled.* The examiner has cited a great deal of old articles to support his assertion that gene therapy is not enabled, but no evidence for why

results obtained with an antibody for the receptor would not be predictive of other molecules which bind.

It is important to note that the claims are limited to conjugates of molecules which bind to the EPCR, and which thereby cause uptake into the cell. This language excludes those molecules which do not have this function.

All of the other components are routine, including the molecules to be delivered, adn the means for coupling a molecule to an EPCR binding agent. Such means are well established in the art and include covalent or ionic interactions; chemical coupling, for example, *via* succinic anhydride; chimeric proteins or protein fusions. Indirect binding may be accomplished *via* an intermediate molecule like streptavidin or biotin, or *via* a positively charged polymer like lysine, pyrrole, or chitosan.

The Examiner is respectfully reminded that the Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B.*

Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art. Coupling means, such as those described above, were well known in the art at the time of filing the present application.

The applicants previously submitted references that clearly show that *gene therapy* was proven to be successful in the treatment of endothelial cells. For example, Baumgartner et al. (Circulation, March 31, 1998; see After Final Amendment and Response mailed on February 4, 2002) demonstrated therapeutic intramuscular gene transfer to endothelial cells in need of treatment using plasmid DNA encoding an endothelial cell mitogen. *Baumgartner explicitly teaches successful gene therapy to endothelial cells*. Baumgartner presents results from a phase 1 trial, "*unanimously approved by the Recombinant DNA Advisory Committee and the U.S. Food and Drug Administration*" (emphasis added) and used to study new chemotherapeutic agents administered to human subjects. *The data presented shows gene expression at the protein level as a transient peak of gene product in the systemic circulation one to three weeks after gene transfer* (see Figure 1 and description at page 1116 of Baumgartner).

The applicants submit that the data of Baumgartner directly refutes the examiner's assertions that 1) studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect; 2) the Recombinant DNA Advisory Committee (RAC) emphasized that expectations of current (per Touchette, as of January 1996, *over two years prior* to the submitted Baumgartner reference)

gene therapy protocols are over sold without any success; and 3) that "gene therapy is considered highly experimental area of research at this time".

The Examiner appears to be concerned with the nature of specific interactions with the EPCR of large blood vessels, given that EPCR "is not limited to endothelial cells of aorta but EPCR is also expressed in abundance in heart and placenta". As stated on pages 9 and 10 of the specification, delivery is enhanced in areas of inflammation or coagulation processes. Serum stimulates nuclear translocation, but is not required. Such conditions are typically more pronounced in the areas where delivery is desired. Thus, a conjugate of the agent binding to the EPCR and the molecule to be delivered that is administered intravascularly, will "congregate" in, and target, areas of inflammation or coagulation. Alternatively, the compositions may be delivered to cell *in vitro*, which can remain in culture or be returned to an individual. The number of molecules to be administered will be determined empirically, based on the efficiency of uptake, the number of cells that will be delivered the composition, and other variable normally considered in determining an effective amount (such as the *in vivo* half-life of the conjugate, and the efficiency of uptake, both of which can be determined without undue experimentation).

Claims 1, 4, 6-7, 9, 10, 13, 14, 18, 19, 21-23, and 25 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner has stated that "[A]t best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR". This is not true - the specification only

demonstrates reduction to practice with a single embodiment, an antibody to EPCR, but other molecules are known, can be made, and could be used. Binding to the endothelial protein C receptor (EPCR) is key to defining the agent as claimed. The specification describes the structure of the claimed agents by providing examples of domains known to interact with the well characterized EPCR (thereby, implicitly illustrating the chemical properties (hydrogen bond acceptor and donor sites arranged specifically of the claimed agents). These elements define the agents based on the claimed interaction with the well defined and characterized EPCR. Although the agents may be organic, inorganic, proteins, or even nucleic acids, specific binding is achieved through complementary interactions (for example, see lines 18-31 of page 5, and lines 1-23 of page 6 of the specification).

"One of skill in the art would have recognized that the spectrum of antibodies which bind to antigens were implicitly disclosed *as a result of the isolation of antigen X*." (emphasis added) Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines"). The appellant respectfully submits that it is well recognized in the art that while antibodies retain the basic Y-shaped molecule structure, composed of two H (heavy) and two L (light) chains, they are differentiated based upon their antigen binding sites (or CDRs). Different binding sites are generated with different amino acid side chains in these positions, which are commonly known in the art as complementarity determining regions, or CDRs, and are located at the end of the variable light and variable heavy chains. It is well established in the art that, based upon the

structural features of antibody recognition of an epitope, at least three forces drive antigen/epitope binding: 1) *hydrogen bonding* between donor-acceptor pairs on the variable regions and the targeted epitope; 2) water molecules that may be present at the antibody-antigen interface contribute to the complex *hydrogen bonding* pattern between molecules; and 3) numerous *van der Waals interactions*. These forces provide for the exquisite complementarity at the interface between the antibody and its targeted epitope. The applicant submits these exact forces are what dictate the structure of the claimed agents. Although the agents may be organic, inorganic, proteins, or even nucleic acids, specific binding is achieved through complementary interactions (see, for example page 5, and the description of CDRs). Therefore, in order for the agent to be delivered to the nucleus of endothelial cells, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location, orientation, and have the correct charge. The identification and characterization of the EPCR, as described in the specification and prior art, by a combination of primary, secondary and tertiary structure analysis is sufficient for the determination of the structure of the agent, or one can simply screen for binding to EPCR, since EPCR is well known to those in the field.. This identification is parallel to the "isolation of antigen X", as stated in the example provided in the written description guidelines and quoted above. Therefore, not only has the targeted EPCR been fully characterized (analogous to the isolation and characterization of antigen X), but the forces that drive the complementary interactions between antibody/antigen and compound/RNA *are the same*. These complementary interactions, as defined by the CDRs (complementarity

determining regions) of antibodies, and the complementary region of the claimed agents define their respective structures (i.e. the CDRs provide specificity to the staggeringly large repertoire of antibodies with different antigen-binding capabilities and are the basis for the immune system's ability to recognize virtually all foreign antigens) in view of their targeted epitope. It is no coincidence that the antibody/epitope and the claimed compound/substrate interactions and structures are defined using the same, well acknowledged and understood term in the art: "*complementarity*". Both, antibodies and nucleic acid hybridizing compounds are now designed based upon *known* epitope/antigen and nucleic acid. Once these "substrate" structures are known, complementary interactions lie at the core of producing a well defined structure that is able to recognize and bind to the target (i.e. like a "lock and key" – see below).

Furthermore, the applicants have disclosed that agents harboring the Gla domain of protein C may be used to direct binding to EPCR (see page 6, lines 12-23), further illustrating just how well characterized endothelial protein C receptor is, and it defines the structure of the agent that targets and binds to them (for example Gla domains). The same issues discussed above, as they relate to complementary interactions, apply to Gla domains.

It will help, perhaps, to view the EPCR as a "lock" and the agent as the "key", wherein the shape of the interior of the lock is defined by hydrophobic, hydrogen bonding, and electrostatic forces provided by the amino acids of the receptor. The key (agent) will only fit into the lock if it is able to "complement" these forces. The analogy to a "lock and key" is an important one because if one can conceptualize the role of the predetermined and defined EPCR

in demanding a specific structure of the binding agent, then one will realize that the compound structure is clearly defined.

As stated in M.P.E.P. § 2173.05(t), which describes the standard to be applied to compounds and compositions, "a compound of unknown structure may be claimed by a combination of physical and chemical characteristics." See *Ex parte Brian*, 118 USPQ 242 (Bd. App. 1958). M.P.E.P. § 2173.05(t) further states that "a compound may also be claimed in terms of the process by which it is made without raising an issue of indefiniteness." The structural features common to the members of the claimed genus can only be determined once the hydrogen bonding arrangement of the target molecule (in this case, EPCR) is derived. Once the "target" is derived, the binding pocket of the EPCR can be easily inserted into any number of commercially available computer programs and the structural features of a binding agent be determined. The structure of the agent is clearly limited based on the requirement for it to be complementary to the EPCR target.

With regard to molecules to be delivered, the Examiner stated that the specification only teaches biotinylated-anti-EPCR antibody and poly-L-lysine conjugated anti-EPCR antibody. The applicants submit that these are merely *examples* of what can be *delivered* to the nucleus of endothelial cells using the claimed methods. The specification clearly describes methods that can be used to determine translocation of molecules to the nucleus. As described at the bottom of page 7 and top of page 8, translocation to the nucleus can be readily assayed using proper and well known reagents that can be detected on the cell and/or in the nucleus of the cell (for

example, surface labeled EPCR and luciferase gene(s) bound to polylysine modified anti-EPCR monoclonal antibodies). As defined by the specification and claims as originally filed, many molecules can be delivered; the key is the molecule binding to the EPCR. One of ordinary skill in the art could readily ascertain, without undue experimentation, whether or not molecules are translocated to the nucleus of endothelial cells. Furthermore, other examples have been presented which clearly illustrate techniques and methods commonly used at the time of filing the present application. For example, the Experimental Procedures section of the specification clearly describes techniques one would/could use to isolate nuclei and nuclear extracts, and assay for translocation of molecules transported *via* EPCRs.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 7, 13, 14 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Each of claims 7, 13, 14 and 19 have been amended to clarify the methods and compositions being claimed. No new limitations were incorporated into the claims.

Rejections Under 35 U.S.C. § 102

Claims 13, 15, 20 and 22 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,225,537 to Foster et. al ("Foster"). Claims 13, 15, 20 and 22-23 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,571,786 to Eibl *et al.* ("Eibl"). Claims 13-15, 20 and 22 were rejected under 35 U.S.C. § 102(b) as being anticipated

by PNAS 93:10212-10216, 1996, to Stearns-Kurosawa *et al.* ("Stearns-Kurosawa"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Foster, et al.

Foster teaches DNA constructs for the expression of hybrid phospholipid-binding proteins, wherein the coding sequences of a phospholipid-binding domain of a lipocortin and a gla-domainless vitamin K-dependent protein are joined. The gla-domain for protein C extends from amino acid 1 of the mature form of protein C to amino acid 45 (see column 7, lines 45-47).

The issue here is whether or not Foster inherently discloses a construct as claimed, of a molecule binding to the EPCR conjugated to a molecule to be delivered.

There is no indication in Foster that one should deliver a hybrid phospholipid-binding protein to large vessel endothelial cells.

Eibl, et al.

Example 3 (see column 6) clearly explains that protein C was *mixed* with thrombin gel and allowed to react (i.e. activate protein C, *not to form a conjugate*). It should be noted that claim 13 is directed, in part, to a "*fusion protein or conjugate* formed by *indirect* binding by a positively charged polymer, chimeric antibody or streptavidin" (emphasis added).

Stearns-Kurasawa

Stearns-Kurosawa describes a fluorescein-labeled anti-mouse IgG to ascertain the effect of antibodies on the binding of fl-APC, fl-cho-protein C, or biotin-PC to E7 cells, EA.hy926 cells, and HUVECs. "

Diagnostic agents have been excluded from claim 14. Therefore Stearns-Kurasawa cannot disclose the subject matter of claim 14.The broadest interpretation of the term "diagnostic", fluorescein-labeled anti-mouse IgG would fall within the scope of a diagnostic agent as defined by amended claim 14 which requires a diagnostic suitable for use in humans. The applicants have enclosed a Merriam-Webster Dictionary definition of the term "diagnosis", wherein version "3a" is directed to an analysis of the nature of a situation <diagnosis of engine trouble>.

The Legal Standard

The legal requirement under 35 U.S.C. § 102(b) is quite explicit: the prior art must disclose each claimed element in a single reference. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 USPF2d 1565 (Fed. Cir. 1995); *cert. denied*, 516 U.S. 988 (195). The disclosure in the reference need not be express, but may anticipate by inherency where it would be appreciated by one of ordinary skill in the art. *Id.*

Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999). Inherency may not be established by probabilities or possibilities. *See Scaltech Inc. v. Retec/Tetra, L.L.C.*, 178 F3d 1378, 51 U.S.PQ2d 1055 (Fed. Cir. 1999). The mere fact that a certain thing may result from a given set of circumstances in not sufficient to establish inherency. *Id.* Where a reference provides a general disclosure such that one skilled in the art would not necessarily recognize that an element is disclosed in the

reference, such a reference is not one that inherently anticipates the element. *See, i.e., Finnigan Corp. v. U.S. Int'l Trade Comm'n*, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999). In relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied reference. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int'f 1990).

Summary

Based on the foregoing discussion, none of the prior art anticipates the claimed conjugates since 1) Foster does not teach a conjugate of a molecule to be delivered to an endothelial cell; 2) one of ordinary skill in the art would readily agree that merely *mixing* protein C with thrombin gel may result in activating protein C, *but would not form a conjugate*); and 3) Stearns-Kurosawa discloses a diagnostic reagent which is excluded from the claim subject matter. Therefore the claims as pending are free from prior art.

U.S.S.N. 09/139,425
Filed: August 25, 1998
AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1-25 is respectfully solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: May 12, 2003

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, May 12, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Aisha Wyatt

Date: May 12, 2003

ATL1 #576667 v1